

Auditory evoked potentials to spectro-temporal modulation of complex tones in normal subjects and patients with severe brain injury

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Summary

In order to assess higher auditory processing capabilities, long-latency auditory evoked potentials (AEPs) were recorded to synthesized musical instrument tones in 22 post-comatose patients with severe brain injury causing variably attenuated behavioural responsiveness. On the basis of normative studies, three different types of spectro-temporal modulation were employed. When a continuous ‘clarinet’ tone changes pitch once every few seconds, N1/P2 potentials are evoked at latencies of ~90 and 180 ms, respectively. Their distribution in the fronto-central region is consistent with generators in the supratemporal cortex of both hemispheres. When the pitch is modulated at a much faster rate (~16 changes/s), responses to each change are virtually abolished but potentials with similar distribution are still elicited by changing the timbre (e.g. ‘clarinet’ to ‘oboe’) every few seconds. These responses appear to represent the cortical processes concerned with spectral pattern analysis and the grouping of frequency components to form sound ‘objects’. Following a period of 16/s oscillation between two pitches, a more anteriorly distributed negativity is evoked on resumption of a steady pitch. Various lines of evidence suggest that this is probably equivalent to the ‘mismatch negativity’ (MMN), reflecting a pre-perceptual,

memory-based process for detection of change in spectro-temporal sound patterns. This method requires no off-line subtraction of AEPs evoked by the onset of a tone, and the MMN is produced rapidly and robustly with considerably larger amplitude (usually >5 μ V) than that to discontinuous pure tones. In the brain-injured patients, the presence of AEPs to two or more complex tone stimuli (in the combined assessment of two authors who were ‘blind’ to the clinical and behavioural data) was significantly associated with the demonstrable possession of discriminative hearing (the ability to respond differentially to verbal commands, in the assessment of a further author who was blind to the AEP findings). Behavioural and electrophysiological findings were in accordance in 18/22 patients, but no AEPs could be recorded in two patients who had clear behavioural evidence of discriminative hearing. The absence of long-latency AEPs should not, therefore, be considered indicative of complete functional deafness. Conversely, AEPs were substantially preserved in two patients without behavioural evidence of discriminative hearing. Although not necessarily indicative of conscious ‘awareness’, such AEP preservation might help to identify sentient patients who are prevented by severe motor disability from communicating their perception.

Keywords: auditory evoked potentials; auditory cortex; brain injury; coma; mismatch negativity

Abbreviations: AEP = auditory evoked potential; EP = evoked potential; MMN = mismatch negativity

Introduction

Recent studies of auditory evoked potentials (AEPs) to synthesized musical instrument tones (Jones *et al.*, 1998; Vaz Pato and Jones, 1999) suggest that particular processes of the human auditory cortex can be activated and differentiated by the scalp potentials produced by different types of spectro-temporal sound modulation. Relatively infrequent (approximately every 2 s) pitch changes of a continuous tone

of ‘clarinet’ timbre evoked N1/P2 potentials which showed little or no variation according to the direction (upward and downward) or magnitude of changes between a semitone and an octave. Similar potentials were evoked by changes of timbre (e.g. ‘clarinet’ to ‘harmonica’ and back) when the pitch was held constant. When pitch changes occurred at higher rates, the associated responses were attenuated

progressively, but potentials were still evoked by infrequently interspersed changes of timbre. This, plus the fact that the N1/P2 to pitch change was attenuated by the presence of an intermittent background tone, to a greater degree when the latter was of the same timbre as the test tone (Jones *et al.*, 1998), suggested that the responses are generated subsequent to the 'grouping' of spectral elements into separate streams representing the individual sound sources (Bregman, 1990). When a tone oscillating between two pitches at 8–16 changes/s suddenly resumed a steady pitch, a negativity with a more anterior distribution was evoked (Vaz Pato and Jones, 1999). Various lines of evidence suggest that this may be equivalent to the 'mismatch negativity' (MMN; Näätänen, 1995; Ritter *et al.*, 1995), a potential which represents detection of change in a sequence of sounds by means of comparison with an image retained in the 'echoic memory' or 'long auditory store' (Cowan, 1984). This process may be of fundamental importance for the extraction of temporal sound information.

Passively elicited evoked potentials (EPs) of this sort present a possible means of investigating the integrity of higher auditory function in behaviourally unresponsive subjects. In comatose patients, abnormality of the short-latency EPs to clicks, diffuse flashes and electric shocks is usually predictive of a poor outcome (e.g. Greenberg *et al.*, 1981; Jordan, 1993; Chiappa and Hill, 1998), but normal responses are not equally predictive of a good functional recovery in the short or the long term (Shin *et al.*, 1989; Keren *et al.*, 1994). This may be because stimuli carrying little or no sensory information fail to engage higher perceptual processes, and hence are inappropriate for assessing brain function at a behaviourally significant level. Long-latency event-related potentials including the P300 are believed to reflect higher 'cognitive' mechanisms, but usually require the active attention of the subject, and hence might be considered applicable only in cases of relatively mild brain injury (Ruijs *et al.*, 1993). There have been reports of P300 and other long-latency potentials elicited in a 'passive' situation (e.g. Rappaport *et al.*, 1990; Gott *et al.*, 1991; Signorino *et al.*, 1997). In severely brain-injured patients, this was achieved most effectively when the 'oddball' stimulus was of a different modality to the 'standards', e.g. a flash as distinct from a tone (Rappaport *et al.*, 1991), but it is debatable whether evidence of discrimination at such a gross level will reflect the patient's ability to make meaningful use of environmental stimuli. Data recently published by Guérit and colleagues (Guérit *et al.*, 1999) suggest that the presence of late potentials following conventional 'oddball' auditory stimuli can be of favourable prognostic significance in comatose patients, but it is not known what these represent in terms of brain processes, nor whether they are likely to have any bearing on the patients' functionality in the longer term.

In the visual modality, most clinical EP studies make use of information-carrying stimuli (usually reversing checkerboards and gratings) rather than unstructured flashes

(e.g. Halliday, 1993). Visual patterns, however, are not easily applicable to severely brain-injured patients whose powers of fixation, accommodation and concentration are impaired. To our knowledge, no-one has yet described methods for recording EPs to information-carrying somatosensory stimuli such as tactile objects and textures. In the auditory modality, Kane and colleagues (Kane *et al.*, 1996) reported that the presence of an MMN to pitch-deviant tones was an accurate predictor of imminent emergence from coma. These findings recently have been confirmed and extended by Fischer and colleagues (Fischer *et al.*, 1999). Listening through headphones requires no active cooperation from the subject, and the MMN is not dependent to a critical degree on voluntary attention (Näätänen, 1995). Using pure tones, however, the signal/noise ratio of the MMN is often found to be so low as to prevent reliable judgement as to its presence or absence. The present study was designed to explore the possibility that AEPs to spectro-temporal modulation of synthesized instrumental tones might prove useful in establishing the functional integrity of the auditory system in brain-injured patients after emergence from coma.

Methods

The patient group comprised 22 post-comatose subjects aged 18–64 years, 12 male and 10 female, who were in-patients of the Royal Hospital for Neuro-disability. Four comatose patients were also tested in the Surgical Intensive Care Unit of the National Hospital for Neurology and Neurosurgery. The control group comprised 14 volunteers aged 20–41 years, eight male and six female, without any history of neurological disease, hearing disorder or head trauma. The post-comatose patients sat in their personal wheelchair and were kept awake for the duration of the recording, but no other instructions were given. The control subjects sat in an armchair and read a book or magazine. The study was approved by the Riverside Research Ethical Committee. Informed consent was given by the controls according to the Declaration of Helsinki, and for the patients according to the consent procedure at the Royal Hospital for Neuro-disability.

The post-comatose patients, who all exhibited spontaneous eye movements and sleep/wake cycles, had suffered severe brain injury as a result of trauma (12), anoxia (nine) or encephalitis (one) at least 9 months before the investigation (Table 1). CT or MRI scans performed soon after the injury provided evidence of cortical or subcortical damage in 16 cases (usually diffuse or multifocal), thalamic involvement in two cases and brainstem involvement in two cases; no imaging information was available in four cases. No patient had evidence of focal damage to peripheral or central auditory structures. Their level of behavioural responsiveness was assessed by one author (R.M.), an occupational therapist who was blind to the electrophysiological findings, using the Sensory Modality Assessment Rehabilitation Technique, methodological details of which have been published (Gill-Thwaites, 1997). The patients were judged

Table 1 Patient data, results of behavioural assessment and AEP scores of two 'blind' assessors (2 = response considered present by both) with N1/MMN latency values when considered definitely present

Case	Sex	Age	Aetiology	Months	SMART		AEP score (N1/MMN latency)			
					Hearing	Motor	Pitch	Timbre	MMN	Overall
1	M	50	A (ca)	20	-	-	1	0	2 (135)	3
2	F	56	T (rta)	16	+	+	2 (80)	2 (105)	2 (108)	6
3	M	58	A (ca)	54	-	+	0	0	0	0
4	M	24	T (fall)	23	+	+	2 (165)	1	2 (180)	5
5	M	32	T (rta)	40	-	-	1	2 (160)	0	3
6	M	36	T (rta)	22	+	+	1	0	0	1
7	M	21	T (n/k)	52	+	+	2 (120)	1	2 (133)	5
8	F	64	A (ca)	19	+	+	2 (100)	1	1	4
9	F	36	A (ca)	20	-	-	1	2 (100)	1	4
10	F	52	T (fall)	13	+	+	2(95)	1	2 (122)	5
11	M	53	A (sah)	91	-	-	1	0	1	2
12	M	32	T (rta)	11	-	-	1	0	2 (99)	3
13	M	25	T (rta)	43	+	+	2 (140)	2 (165)	2 (160)	6
14	M	22	A (hanging)	52	-	-	1	n/a	n/a	1 (3)
15	M	18	Encephalitis	9	+	+	1	2 (89)	1	4
16	F	47	A (ica)	7	+	+	1	2 (90)	1	4
17	F	55	T (rta)	10	-	-	1	1	1	3
18	M	58	A (ica)	18	+	+	2 (167)	2 (135)	1	5
19	F	26	A (insulin o/d)	42	+	+	2 (108)	0	1	3
20	F	30	T (rta)	15	+	+	2 (109)	1	2 (129)	5
21	F	42	T (fall)	16	-	-	2 (88)	1	1	4
22	F	25	T (rta)	10	-	-	1	0	1	2
Control group mean latency (ms)							93	107	99	
Normal limits (mean \pm 2.5 SDs)							123	133	115	

A = anoxia; T = trauma; ca = cardiac arrest; ica = intracranial aneurysm; rta = road traffic accident; sah = subarachnoid haemorrhage; o/d = overdose; n/k = not known; n/a = not assessed; SMART = Sensory Modality Assessment Rehabilitation Technique; + = evidence of discriminative hearing or purposeful movement on SMART.

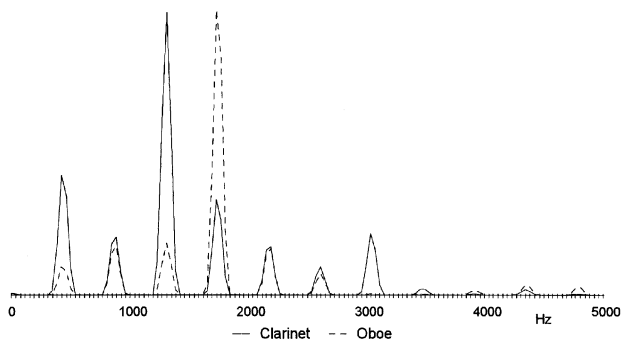
to be capable of discriminative hearing (and also of volitional movement) if they were able to respond appropriately to specific commands such as 'close your eyes', 'press the buzzer once', etc. Some patients showed variable responsiveness on repeated examination, and the best results obtained within ~1 month of electrophysiological testing were used for correlation.

Four recording electrodes were attached to the scalp at locations Fpz, Fz, Cz and Pz of the 10-20 system and the contact impedance was reduced to <5 k Ω . The reference electrode was on the dorsum of the neck at the base of the skull. To ensure the gross integrity of the afferent auditory pathway, in 20 patients short- and middle-latency AEPs were recorded to clicks ~65 dB above the threshold of normally hearing control subjects, presented binaurally at 6/s. The EEG was amplified with a bandpass of 10 Hz-1 kHz (corner frequencies), sampled at 8.33 kHz for 60 ms (1401 Plus analogue-to-digital converter, Cambridge Electronic Design Ltd, Cambridge, UK) starting 2 ms after the stimulus in order to exclude the stimulus artefact, and four average responses were computed, each of 500 stimuli.

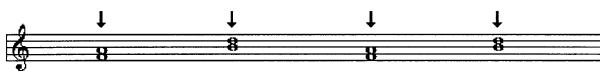
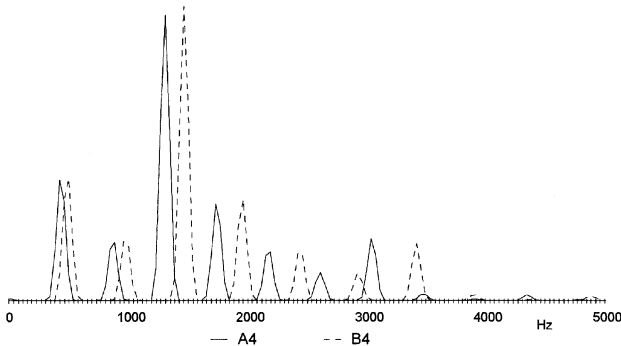
Long-latency AEPs to complex tone modulation were recorded using the same electrode locations. The EEG was amplified with a bandpass of 1-200 Hz and sampled at 1 kHz for an epoch of 500 ms starting 20 ms before each stimulus

change for the patients, 50 ms before stimulus change for the controls. Different although functionally similar signal acquisition programs were used: 'SIGAVG' for the patients, 'SIGNAL' for the controls, both produced by Cambridge Electronic Design Ltd, Cambridge UK. Musical instrument tones were synthesized by an MU10 tone generator (Yamaha Corporation, Hamamatsu, Japan) and controlled by an IBM-compatible notebook PC. The software used to construct and play stimulus sequences was Cubasis (Steinberg Soft & Hardware GmbH, Hamburg, Germany). The left and right audio channels were split in order to use one channel for stimulation (presented to both ears) and the other to trigger the recording apparatus. The tones were continuous, changes of pitch and timbre occurring smoothly with a transition period of ~20 ms (established by examination of their waveform envelopes; this was also done to establish the precise temporal relationship between stimulus and trigger). The 'clarinet' and 'oboe' timbres were chosen because of their clear distinction, unexaggerated onset and subsequently steady intensity and pitch. Their spectra were determined by analogue-to-digital conversion and fast Fourier analysis software (Pico Technology Ltd, Cambridge, UK). Tones of A4 pitch had a fundamental frequency of 440 Hz and the intensity employed was 45-50 dB above the threshold of the control subjects. Harmonics of the fundamental were present

Spectra of 'clarinet' and 'oboe' timbres, A4 pitch



Spectra of 'clarinet' tones, A4 and B4 pitch



Stimulus 1: pitch change of two simultaneous 'clarinet' tones every 2 s



Stimulus 2: timbre change every 2 s during 16/s pitch changes



Stimulus 3: end of 2 s of oscillation between A4 and B4, at time of next expected change

Fig. 1 Frequency spectra and musical notation of the stimuli used in the study. Arrows indicate the timing of trigger pulses for commencement of the averaging epochs.

in proportions which differed between the two timbres but remained relatively constant at different pitches (Fig. 1).

Three stimulus sequences were employed (Fig. 1). Stimulus 1: pitch change (Jones *et al.*, 1998). In order to cover a wide band of the frequency spectrum, two 'clarinet' tones were presented simultaneously; one changed pitch from *F4* to *B4* and back and the other from *A4* to *D5* and back every 2 s. Stimulus 2: timbre change during a sequence of

rapid pitch changes. In pilot studies (Jones, 1999), change from 'clarinet' timbre to 'oboe' and back every 2 s elicited consistent potentials when the pitch changes occurred at 16/s within a band of six semitones (*G4*–*C5*). Stimulus 3: end of oscillatory pitch changes (Vaz Pato and Jones, 1999). For 2 s, the 'clarinet' tone oscillated between the notes *A4* and *B4* at 16 changes/s, before coming to rest on *B4* for 0.5 s.

For each stimulus, four averages of 50 responses were made and subsequently averaged together, excluding any with excessive artefact. Amplitudes and latencies were measured from the pre-stimulus baseline and the time of stimulus change, respectively. In the control group, the amplitude distributions of the major negative potentials (N1 with stimuli 1 and 2, MMN with stimulus 3) were compared using multivariate ANOVA (analysis of variance). The AEPs of the patients were evaluated by two authors (M.V.P. and L.S.) who acquired and analysed the control data, but had no contact with or individual knowledge of the patients. Their assessments for each stimulus (1 = present, 0 = absent) were made independently of one another and added together to give a maximum AEP score of 2 for each stimulus, 6 for each patient. The association between the total AEP score and the results of behavioural auditory assessment was evaluated using the χ^2 test.

Results

Control data

In the control group, N1/P2 potentials to pitch change and the MMN at the end of pitch oscillation were present in 14/14 subjects, while the N1/P2 to change of timbre during rapid pitch modulation was present in 13/14 subjects (group mean waveforms are shown in Fig. 2). At Fz, the N1 to pitch change measured $7.1 \pm 3.3 \mu\text{V}$ (mean \pm standard deviation) at a latency of 93 ± 12 ms. At the end of pitch oscillation, the MMN measured $5.9 \pm 2.4 \mu\text{V}$ at 99 ± 6.5 ms (relative to the expected time of occurrence of the next pitch change). The N1 to timbre change, when present, measured $3.9 \pm 1.8 \mu\text{V}$ at 107 ± 10 ms. The amplitude distribution of the negative peak at the four midline sagittal electrodes differed amongst the three stimulus conditions; in multivariate ANOVA, the interaction between electrode location and stimulus condition was significant [$F(3,2) = 8.4, P < 0.001$], the major difference being between the N1 to pitch change and the MMN at the end of oscillation which was distributed more anteriorly. N1 to timbre change had a distribution more closely resembling that of the pitch change N1.

Patient data

In 14 patients out of 20, middle-latency AEPs Na, Pa and Nb were identifiable at latencies between 20 and 50 ms after binaural click stimulation. In a further three patients, only a single negative peak was present. Brainstem component V was present at ~ 6 ms in every case.

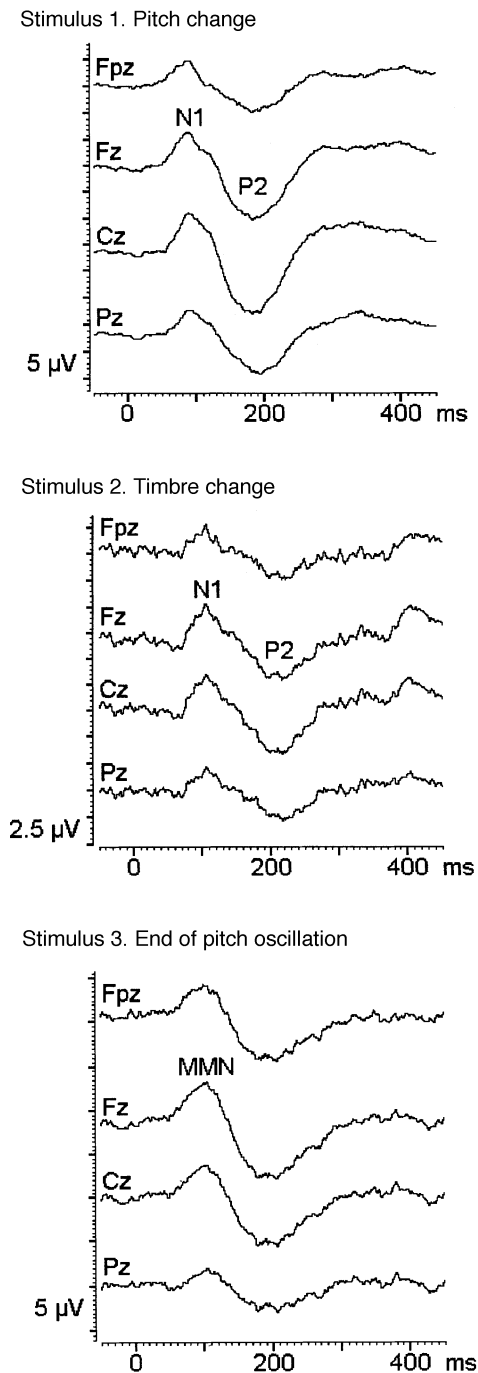


Fig. 2 Mean long-latency AEPs of 14 control subjects to the three complex tone stimuli. The N1 to pitch and timbre change were distributed more posteriorly on the scalp than the MMN at the end of pitch oscillation, consistent with a generator situated more posteriorly in the supratemporal cortex.

In the preliminary study of four unselected, comatose patients, no consistent long-latency AEPs could be recorded in two. In one patient, consistent N1/P2 potentials were obtained to pitch change, while responses to the other two stimuli were absent. Apparently normal responses to all three stimuli were recorded in the fourth patient who was beginning to show signs of responsiveness.

According to the 'blind' AEP assessment of the post-comatose patients, two had definite responses (i.e. present in the opinion of both assessors) to all three stimuli (AEP score = 6, Table 1), five had definite responses to two and equivocal responses to one stimulus (AEP score = 5) and a further three had definite responses to one and equivocal responses to two stimuli (AEP score = 4). Six patients were accorded an AEP score of 3 (including one in whom only the pitch change stimulus was applied with equivocal result), two patients had an AEP score of 2, one a score of 1 and one a score of 0. Most often preserved was the N1 to pitch change (total score in the patient group 31/44, as compared with 26/42 for the MMN and 21/42 for the timbre change N1). No patient had a definitely preserved N1 to timbre change and/or a preserved MMN in spite of an absent N1 to pitch change. There was minimal evidence of dissociation between the timbre change N1 and the MMN, two patients having a clearly preserved MMN while the N1 to timbre change was absent, and one the converse finding. Where AEPs were present in the opinion of both assessors, the negative peak was prolonged in latency (>2.5 SDs above the mean of the control group) in 3/10 patients for pitch change, 3/7 for timbre change and 6/8 for the MMN (see Table 1).

The percentage of patients with behaviourally evident discriminative hearing (i.e. the ability to respond differentially to verbal commands) increased monotonically with AEP scores up to 2 (0%) through 3 (17%) and 4 (60%) to 5 or 6 (100%). The association between discriminative hearing preservation and an AEP score of 4 or more was significant ($\chi^2 = 6.45$, $P < 0.02$). Four individuals failed to conform to this association, two in whom AEPs were 'false positive' for hearing preservation and two 'false negative'. In one of the latter, a repeat study again failed to demonstrate any definite long-latency AEPs, although on both occasions the patient was capable of limited two-way verbal communication.

The mean AEP score in 12 patients whose brain injury was due to trauma was not significantly different from that of the 10 patients with anoxic or encephalitic brain damage (mean scores of 3.6 and 3.2, respectively). The incidence and number of delayed AEPs was greater in the trauma cases (incidence 6/12, 10/17 AEPs delayed) as compared with the remainder (incidence 2/10, 3/8 AEPs delayed), but the differences were not statistically significant.

Individual cases

Case 1, who suffered hydrocephalus and subarachnoid haemorrhage in conjunction with a myocardial infarction, appeared awake and composed, but showed no evidence of discriminative or localizing sensation in any modality, nor any evidence of purposeful movement. The N1 to pitch change was only present intermittently, but an MMN was present with prolonged latency in the opinion of both AEP assessors (Fig. 3). This confirmed the findings of a study made 1 year earlier at the National Hospital for Neurology

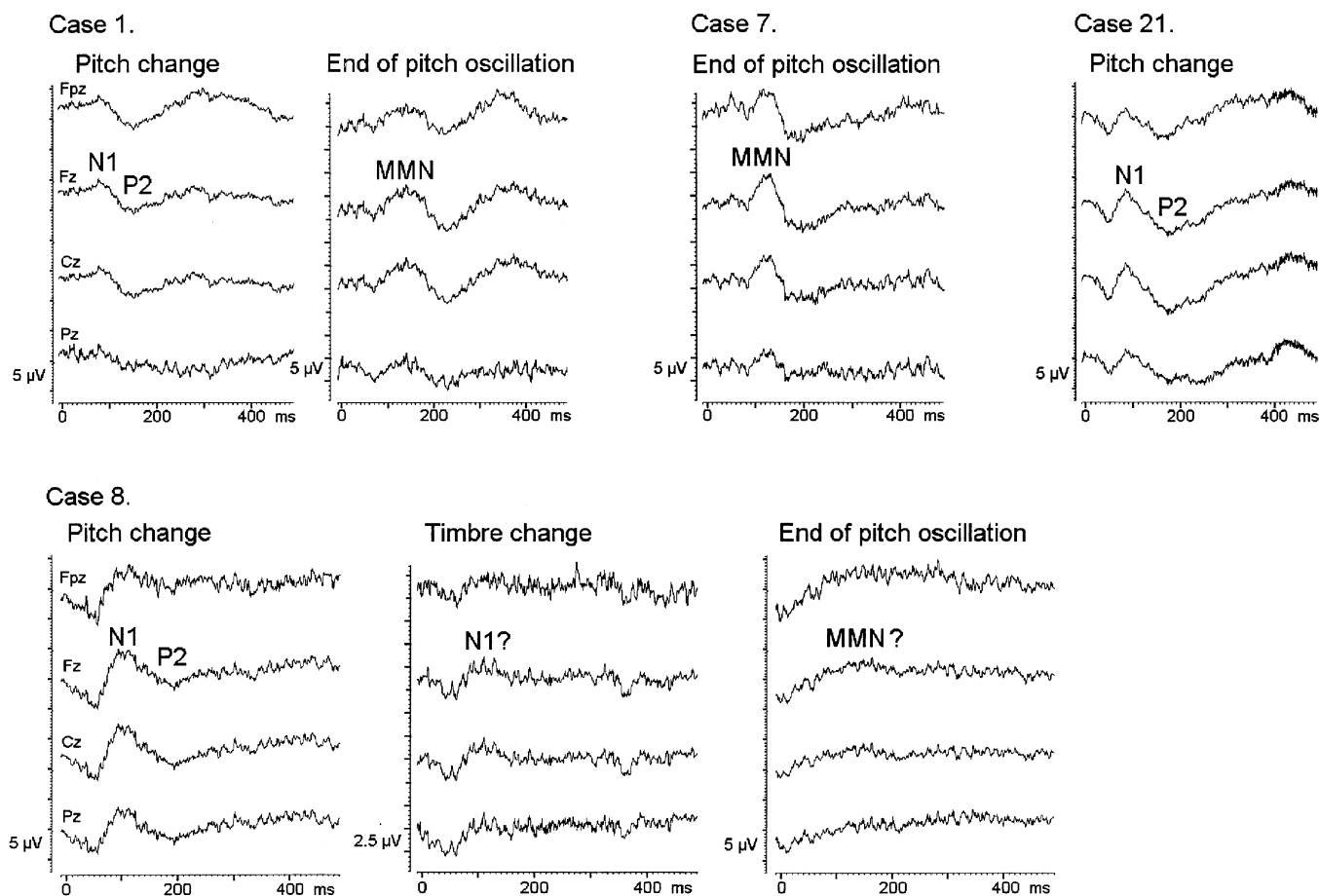


Fig. 3 Example AEPs of the patient group. In Case 1 (no evidence of discriminative hearing), the N1/P2 to pitch change was only present intermittently and the timbre change response (not illustrated) was absent, but the MMN was recorded consistently on two occasions. Case 7 (capable of discriminative hearing) had preserved MMN and also (not illustrated) preserved N1/P2 to pitch change and equivocal N1/P2 to timbre change. In Case 8 (capable of discriminative hearing), the N1/P2 to pitch change was considered present by both assessors, while the N1 to timbre change and the MMN at the end of oscillation were equivocal. Case 21 (no discriminative hearing) had preserved N1/P2 to pitch change, while the other two responses (not illustrated) were equivocal.

and Neurosurgery, when the patient's behavioural status had been similar.

Case 2 had suffered mainly left-sided head injury as a pedestrian involved in a road traffic accident. She inconsistently exhibited purposeful movements and the ability to respond to auditory commands, with some spontaneous communicative vocalization, but there was no evidence of discriminative sensation in the other sensory modalities. AEPs were considered definitely present and of normal latency to all three stimuli. Similar findings had been obtained 1 year earlier at the National Hospital for Neurology and Neurosurgery, shortly before the patient emerged from coma.

Case 6 suffered diffuse haemorrhagic brain damage following a road traffic accident. At the time of testing, he had made a considerable recovery, possessed discriminative sensation in all sensory modalities, was capable of two-way verbal communication and exhibited purposeful movements (e.g. self-feeding). However, in spite of good cooperation, no definite long-latency AEPs could be recorded on two separate occasions.

Case 7 suffered a right-sided and basal skull fracture with subarachnoid haemorrhage, possibly as a result of an assault. Although severely motor impaired and superficially unresponsive, after >1 year in another institution he had been discovered to understand speech and was able to communicate by means of a button-press located against his body. N1 to pitch change and MMN were considered definitely present (MMN slightly prolonged in latency, Fig. 3), N1 to timbre change equivocally so.

Case 8 suffered a cardiac arrest, anoxic brain damage and transient renal failure secondary to septicaemia from a pelvic abscess. At the time of testing, she showed semi-purposeful movements of the head (nodding and shaking) and left upper limb (reaching for an apparently imagined object). On behavioural assessment, depending on her level of arousal, she intermittently would respond correctly to simple commands such as 'look up'. Stimuli of other modalities only elicited orientation and/or withdrawal. The N1 to pitch change was considered definitely present, the timbre change N1 and MMN equivocally so (Fig. 3).

Case 14 had been discovered hanging, and exhibited severe global brain atrophy on CT. On behavioural assessment, there was no evidence of purposeful movement, sensory discrimination, localization or withdrawal in any modality. The N1 to pitch change was equivocally present, but the test had to be curtailed on account of the patient's uncontrollable movements.

Case 21 suffered a left-sided subdural haemorrhage following a fall. She showed the ability visually to track a moving object, but otherwise exhibited only reflex motor activity and withdrawal from loud sounds with inconsistent habituation. The N1 to pitch change was considered definitely present (Fig. 3) and the timbre change N1 and MMN equivocally so.

Discussion

Finding an ecologically valid approach to the neurophysiology of the auditory cortex

The clicks and disconnected pure tones used for much electrophysiological research on the auditory cortex, both human and animal, carry little information and bear little resemblance to sounds of the environment or those used for communication. Consequently, it is not surprising that such studies have failed to lead to clear insights into the mechanisms of sound perception at this level. In recent years, there has been some shift away from the physical, Helmholtzian view of hearing, to one which is more behaviourally oriented (Masterton, 1992), and this has led some researchers (e.g. Wang *et al.*, 1995) to look for representation in the auditory cortex of species-specific vocalizations. However, considering the very limited use many animals make of sound for communication, it seems unlikely that this is the main purpose for which the auditory cortex has evolved. Consideration of the divergent course of mammalian evolution also raises major doubts concerning the validity of attempts to uncover the underlying processes of human speech perception in the auditory cortices of monkeys (e.g. Steinschneider *et al.*, 1995) or even more distantly related species such as cats (e.g. Eggermont, 1995; Schreiner, 1998) and ferrets (Versnel and Shamma, 1998).

Far more universal than complex auditory communication is the use of sound for orientation in the environment, self-preservation and identification of prey. To this end, it is clearly of importance to be able to discriminate individual sound 'objects' from the background. Since the cochlea effectively deconstructs sound into its spectral components, the work of the central auditory system must be essentially reconstructive, 'grouping' the spectral elements into distinct streams simulating the original sources (Bregman, 1990), estimating the location of those sources in external space and analysing their temporal changes for potentially important information. Investigation of these processes may be addressed profitably at the level of neuronal populations (AEPs) as well as single units. Synthesized musical instrument

tones make a convenient tool since, although the pitch of most environmental sounds is ill-defined, they all possess 'timbre' which should be identifiable by processes of spectral pattern analysis. How much of this analysis occurs at the cortical as distinct from the subcortical level is uncertain, but the elicitation of N1/P2 potentials by pitch and timbre modulation of complex tones does seem to indicate that such a process has occurred (Jones *et al.*, 1998).

AEPs to complex tone modulation

In our previous studies (Jones *et al.*, 1998; Vaz Pato and Jones, 1999), we investigated various types of complex tone modulation giving rise to negative scalp potentials peaking at ~100 ms. Infrequently occurring pitch changes of a continuous tone produce an N1 which is maximal between the vertex (Cz) and the mid-frontal electrode (Fz) and symmetrically distributed over the two hemispheres. This is preceded by a less consistent P1 and followed by a large P2, peaking at ~180 ms. A small negative/positive 'T-complex', ~50 ms longer in latency, was recorded at lateral temporal electrodes. This was larger over the right hemisphere in almost all right-handed subjects and showed the converse laterality in ~25% of left-handers (Jones and Byrne, 1998). The right temporal cortex has been implicated in musical timbre discrimination (Samson and Zatorre, 1994) but, since the T-complex is often of very low amplitude in normal subjects, it was not examined in the present study.

Infrequent changes in the timbre of a continuous tone give rise to similar N1/P2 potentials and a T-complex, whether the pitch of the tone is steady or in a rapid state of modulation such that the responses to each individual pitch change are virtually absent. This suggests a more general mechanism for spectral pattern analysis which is able to discriminate between pitch modulation of an existing timbre (or object) and the onset of a new one. Although the optimal conditions for timbre change to elicit an N1 in a pitch-modulated tone have yet to be determined, it appears to be necessary for the pitch variation to be within a relatively narrow band of a few semitones (timbre change is also subjectively harder to detect when pitch varies rapidly over a wider range). It would also be necessary for the pitch-modulated tone to be collated over a period of time in order to identify its timbral constancy.

A number of psychophysical phenomena including the perceptual 'persistence' of very brief sounds and the backward and forward masking of a quiet sound by a louder one suggest the existence of a 'short auditory store' whose duration is in the order of 200 ms (reviewed by Cowan, 1984). In our own studies, by varying the gaps between tones alternating between two different timbres, it was shown that the process giving rise to the timbre change N1 and (particularly) the large following P2 only starts to operate when the gaps are less than ~200 ms (Jones *et al.*, 1998). Yabe and colleagues reported that the magnetic counterpart of the MMN is only elicited by the omission of a brief tone from a train of identical tones when the stimulus onset

asynchrony is <175 ms (Yabe *et al.*, 1998). This might be interpreted as the maximum interval over which physically discontinuous sounds can, under certain circumstances, be treated as if they were continuous. If it is the function of the short auditory store to integrate sounds over this period, one reason for the integration may be so that the immediate sound can be compared with the changing spectral structure of the previous ones, in order to be able to identify when a new timbre has commenced.

At the end of a period of rapid oscillation between two pitches or, it appears, any rapid sequence lasting a few seconds, a negative peak is evoked on resumption of a steady pitch (Vaz Pato and Jones, 1999). Its scalp distribution was anterior to that of the N1 to pitch or timbre change, but similar to that of the MMN elicited in the conventional way by discontinuous tones. The amplitude of the conventional MMN, however, was markedly smaller. By varying the rate of changes, the latency of the negative peak at the end of pitch oscillation was shown to be fairly constant, not with respect to the last change of pitch which actually occurred, but with respect to the next change, which failed to occur. A very large body of evidence (reviewed by Näätänen, 1995; Ritter *et al.*, 1995) suggests that the MMN is generated automatically (i.e. without the necessary application of voluntary attention) by the occurrence of a 'deviant' sound differing in any one of a number of dimensions (pitch, intensity, source location, etc.) from a preceding series of identical 'standards'. The MMN therefore also represents the output of a process of comparison between the incoming sound and an image or template of the previous ones, apparently located more anteriorly in the supratemporal cortex than the process of spectral analysis involved with pitch and timbre discrimination. The maximum interval between discontinuous sounds which are still capable of eliciting an MMN is in the order of a few seconds, comparable with the duration of the 'echoic memory' or 'long auditory store' (Cowan, 1984). Apart from the duration over which sounds are retained, an important difference between the short and the long store is that whereas in the former each new sound tends to 'overwrite' the representation of the previous one (or at least become integrated with it, their temporal relationship becoming obscured), in the long store the temporal relationships between sounds are retained. The long store may therefore represent a stage in the process by which sounds are analysed for their temporal structure and information content. The MMN evoked at the end of a period of rapid pitch modulation of a complex tone has a larger amplitude and a shorter latency than the MMN conventionally elicited by disconnected, pure tones, possibly because the image contained in the long auditory store has had no opportunity to decay, or perhaps owing to the summation of mismatch potentials associated with each frequency component of the complex tone. Generation of the MMN at the moment of non-occurrence of an expected change has a further implication for the role of the long auditory store—

that of synthesizing a model of the sound modulation pattern which is effectively projected into the future.

Assessment of brain-injured patients

At the Royal Hospital for Neuro-disability, the Sensory Modality Assessment Rehabilitation Technique has been developed by the Occupational Therapy department for application to post-comatose, severely brain-injured patients in order to establish their level of responsiveness in each sensory modality (Gill-Thwaites, 1997). By emphasizing the modality showing the highest degree of functional preservation, rather than the mean across all modalities, it appears that some patients who are superficially 'unresponsive' may, in fact, possess a higher level of cognitive function than that suggested by the Western Neuro Sensory Stimulation Profile (Ansell and Keenan, 1989). However, behavioural sensory assessment is only possible when the patient is able to indicate when a stimulus has been perceived. Some patients who are fully or partially sentient may be prevented from communicating this by their motor impairment. AEP assessment, on the other hand, offers a means of ascertaining a patient's higher auditory processing capacity irrespective of any motor disability, and might help identify those who may be capable of understanding speech. However, the presence of AEPs to complex tone modulation should not be considered indicative of conscious 'awareness'. Long-latency AEPs including the MMN are elicited without the need for voluntary attention, hence subjects may have no conscious perception of each stimulus change. Also, although our experience of comatose patients is small, it also seems to be possible for long-latency AEPs to be normal in this state.

The two methods of classification, the behavioural assessment inescapably subjective, but the AEP score made fully objective by the use of 'blind' AEP assessors, achieved agreement in 18 out of 22 patients. The criterion of AEP preservation was a majority score (more responses considered to be present than absent) while that of hearing preservation was the ability to understand and respond to verbal instructions. In future, however, it may be desirable for AEP assessment to incorporate relevant information about the patient, particularly as regards compliance with the examination, level of alertness and the extent to which recordings may have been contaminated by movement artefacts. One patient was excluded from the study because he was unable to tolerate the presence of electrodes on his head, in another the session was curtailed on account of excessive facial and body movements, and in others the quality and reproducibility of the recordings was sub-optimal for similar reasons. The important issue as to how reproducible are the AEPs obtained on different occasions by different examiners will be addressed in future studies.

Although we have yet to encounter a normal subject with completely unrecordable AEPs, in one of the patients the N1 and MMN were virtually absent although he was clearly capable of understanding speech and was alert throughout

the test. Repeat recordings made 2 months later also failed to reveal any definite long-latency potentials. Clearly, the absence of potentials in patients with diffuse brain damage cannot be regarded as an infallible indicator of functional deafness. Two patients had an AEP score of 4 (meaning a definite response to one and an equivocal response to two stimuli) in spite of no behavioural evidence of auditory discrimination, and a further five 'non-discriminating' patients had AEP scores of 3, just below the arbitrary level which was found to correlate with discriminative hearing preservation. Behaviourally, all seven of these patients also failed to show any capability of purposeful movement, so it is conceivable that some such as these may be prevented by their motor disability from communicating their perception. One patient with an AEP score of 5 was capable of understanding speech and of communicating by button-press, but had in another hospital been diagnosed 'unresponsive' for more than a year while he was (retrospectively self-reported to be) conscious and fully sentient of speech sounds. The dependence of behavioural multi-sensory assessment on sensory *and* motor integrity is emphasized further by the fact that no patient in this study who was considered to be incapable of purposive movement was judged to be capable of discriminative hearing. This unavoidable deficiency in behavioural assessment is one which electrophysiological methods are particularly well qualified to address.

The possibility of focal involvement of auditory structures could not be excluded absolutely in every case, but the preservation of brainstem and middle-latency potentials ensured the gross integrity of the pathway from the cochlea to the cortex, at least on one side of the brain, in the majority. Although most of the preserved responses to pitch and timbre change were of normal latency, 75% of the MMNs were delayed abnormally and the incidence and number of delayed AEPs tended to be greater amongst cases of traumatic brain injury. It may therefore be appropriate to consider the role of distributed neuronal circuits in the temporal processing of sounds. Reverberatory interaction between cortical and subcortical regions (specifically the auditory nuclei of the thalamus) may be necessary in order to retain information in the long auditory store, and such circuits may be particularly vulnerable to shearing caused by head trauma. Alternatively, a perturbation of internal 'clocks' necessary for temporal calibration of sounds contained in the long store might result in a breakdown of spectro-temporal analysis mechanisms (Jones, 2000). This area of research is at an early stage of development, and further investigation into the complex tone AEPs of normal and brain-lesioned subjects may lead to new insights into the higher processes of auditory perception.

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